A rational approach to drug treatment in psychiatry

Joanna Moncrieff, Nov 2011,
The Myth of the Chemical Cure
A Critique of Psychiatric Drug Treatment
Joanna Moncrieff
A STRAIGHT TALKING INTRODUCTION TO

PSYCHIATRIC DRUGS

JOANNA MONCRIEFF
# Models of drug action

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Psychoactive drugs

• Produce altered mental states
• Physical effects too
• Tolerance
• Withdrawal effects
• “spell binding” (Breggin, 2007)
Drugs used prior to 1950s

- barbiturates
- hyoscine
- paraldehyde
- opium
- bromides
- benzedrine
- amphetamine
Insulin coma therapy

“the introduction of insulin coma treatment was from a historical point of view the decisive step from a purely symptomatic to a curative therapy of the endogenous psychoses.”

Ehrhardt, 1966
ECT and depression

• “a specific and adequate means to relieve this common illness” (involutional melancholia) (Moss et al, 1953).

• Stimulated an underactive pituitary gland (Sadler, 1953)

• Rectified abnormal brain circuits (Paterson, 1963)
Kilogrammes of Chlorpromazine used in French Hospitals 1952-1957 (J. Swazey, 1974)
Specificity of neuroleptics

• “they appear to do more than tranquilise” (Henderson & Gillespie 1962).

• “the drugs penetrate much closer to the site of mechanism of the disease itself than any other procedure applied hitherto” (Mayer-Gross, Slater, & Roth 1960).
Tyrant in the house?

‘Thorazine’ can control the agitated, belligerent senile
and help the patient to live a composed and useful life.

When ‘Thorazine’ is administered to the agitated senile, there is a marked decrease in
his nerve-racking outbursts of hostility, irritability, abusiveness, incessant talking and
“day-and-night” pacing or restlessness.

On ‘Thorazine’ therapy, the patient often forms more regular eating and sleeping
habits and improves in his personal hygiene. As the patient becomes more tractable
and cooperative, he is able to live a composed and useful life.

THORAZINE*
chlorpromazine, S.R.S.

one of the fundamental drugs in medicine

Smith Kline & French Laboratories, Philadelphia

in acute schizophrenia

Melleril

strikes promptly at the target symptoms:
disorders of thought, affect, behaviour and perception

Melleril is a major tranquilliser with an impressive clinical record in the treatment of acute schizophrenia. Response to Melleril is rapid and predictable. Within 24 hours a tranquilising effect occurs. Within 3-4 days the patient becomes calm, cooperative and sociable. Within 7 days target symptoms begin to respond. An important aspect of Melleril therapy is to start with an adequate "loading" dose. Full information on Melleril, including dosage details and clinical warnings, will be supplied on request. Tablets of 50 mg, 75 mg, and 100 mg. Thiosulphate Hydrochloride B.P. Also available: Syrup.

there is no anti-psychotic more effective than Melleril

Sankyo Products Limited, Sankyo House, 20 Great Castle Street, London, W1R 8AE

Vitalk is a registered trade mark.
Specificity of antidepressants

- antidepressants “appear to act specifically against depressive symptoms” (Dally, 1967)

- “much more specific” than stimulants (Psychopharmacology conference 1962, Goldman, (1966),
Changes in Therapeutic Concepts

Pre 1950s:
- Sedatives
- Stimulants

Post 1950s:
- Antipsychotics
- Antidepressants
- Anxiolytics
- Mood stabilisers
- Hypnotics
Evidence

Placebo controlled trials do not distinguish disease-centred from drug-centred model

RCTs confounded by psychoactive effects which may:
• Impact on expression of symptoms included in rating scales
• Subvert the double blind, introducing expectancy (placebo) effects
• Cause their own undetected impairments
Evidence for disease-centred model of drug action

But disease-centred model might be supported if:
• Pathology of disease explains drug action
• Supposedly specific drugs better than non specific ones
• Animal tests select specific drugs
A drug centred approach: some drug-induced psychic effects

- Euphoria
- Sedation- different types
- Emotional flattening
- Relaxation
- Stimulation
- Psychedelic effects
- Cognitive slowing and impairment
- Reduced emotional sensitivity
Information needed to develop a drug centred practice

- The total profile of a drugs actions- what neurological and bodily state does it produce? What does it feel like to take it?
- Long-term effects of drugs- including tolerance and withdrawal effects, physical effects and psychological effects
- Are the effects a drug produces useful in an individuals particular situation?
- Do they out-weight the disadvantages?
Example: neuroleptics
(antipsychotics)
Delay and Deniker 1952

“the apparent indifference, or delay in response to external stimuli, the emotional and affective neutrality, the decrease in both initiative and preoccupation without alteration of conscious awareness or in intellectual faculties, constitute the psychic syndrome due to treatment”
Experimental neurological syndromes and the new drug therapies in psychiatry

‘From the beginning it was evident that no lines of demarcation could be drawn between therapeutic degrees of reduced psychomotor activity and early symptoms of parkinsonism...What we witnessed were gradual transition from hypermotility to hypomotility, which, in a certain proportion of patients, progressed to the more pronounced degrees of parkinsonian rigidity. Clinical evidence therefore, indicated that the therapeutic function of chlorpromazine and reserpine could not be separated from their modifying influence on the function of the subcortical motor system in transacting volitional, affective and intentional functions’ (Freyhan, 1959) (P10).
The subjective experience of taking antipsychotics medication
Moncrieff et al, 2009. From askapatient.com

- “extremely hard to move, think, talk” (haloperidol)
- “heavy mental and physical stagnance” (haloperidol)
- “emotionally empty, dead inside” (trifluoperazine)
From askapatient.com

• “no emotions, only a weird, spacey, empty feeling, no arousal, no excitement, no joy, nothing” (risperidone)

• “I’ve never been able to eat as much as I did when I was on Zyprexa. I gained 40lbs in no time and my mind was in a constant fog of lethargy and indifference. I didn’t care about anything. I just wanted to sit around and eat.” (olanzapine)
“decreased the intensity of inner voices” (risperidone)

“stops my negative thoughts and feelings being amplified and overwhelming me” (risperidone)

“hypersomnia (increased sleeping), calming of moods, general smoothing out of mania, calmness, less hallucinations” (olanzapine).
“Although I felt very well, I felt as if I had absolutely nothing to talk about. I kept wondering about whatever [it] was that had been so interesting during most of my life that I had suddenly lost… But I was very much in contact with reality and for that I was thankful” (haloperidol)
• “it makes me feel like a veggie, but that was better than what I was going through and it kept me out of the hospital” (olanzapine)
A drug centred approach to treatment of psychotic disorders

- Effects may be useful to suppress acute symptoms
- Other sedatives may be useful as well
- Not necessary in everyone

- Side effects may outweigh advantages of long-term treatment
Example: antidepressants
Psychoactive effects of “antidepressants”

Tricyclic antidepressants:

• Complex effects on numerous neurotransmitter systems
• Profound sedation
• Cognitive and motor impairment
• EEG slowing
• Dysphoria
• Some have dopamine blocking activity at higher doses
Psychoactive effects of SSRIs and venlafaxine

- Sedative effects
- Cognitive impairment
- Emotional blunting
- Reduced libido
- Arousal/activation effects
- Emotional instability
- Not euphoriant (like stimulants or benzodiazepines)
- Not relaxant like benzodiazepines
- Suicide-inducing
Psychoactive effects of antidepressants:
(askapatient.com)

• “Increased anxiety initially, borderline panic, mild insomnia, listlessness and lethargy” (Fluoxetine).
• “Total loss of libido, sometimes suicidal, loss of appetite, inability to care about anything, mood swings” (Fluoxetine).

• “Fuzzy memory..loss of libido.. general numbness/mental blankness…memory loss” (venlafaxine).
• “Sleepy all the time, suicidal thoughts, irritability, don’t care about anything” (venlafaxine).
A drug-centred approach to treating depression

- No evidence that any drug can specifically reverse or ameliorate depression or depressive feelings
- Many drugs suppress mental activity and emotions- neuroleptics, ? SSRIs
- Sedatives may be useful to help insomnia, anxiety and agitation
- But…people may prefer alternative strategies!
Patient information

- The antidepressant will help normalise your serotonin levels
- The antidepressant will improve your depression
- The drug affects the way people think and feel (not just people with depression), but we are not sure how. It may dampen down your emotions, and make you feel mildly drugged or groggy.
“Mood stabilisers”

• Lithium tested in acute mania, but not specific

• Lithium and some other drugs reduce relapse in manic depression (BP 1) more than placebo in withdrawal trials
Drug centred approach to treating manic depression

- Sedatives useful for mania
- Sedatives may be useful for prophylaxis, but evidence inconclusive so far.
- Whether to use them long-term depends on balancing the possible small reduction in risk of relapse with the consequences of long-term sedative therapy.
Advantages of drug centred model

• More democratic and patient centred. Patients have to find drug effects useful
• More cautious. Balance of benefits and adverse effects is different.
• More transparent: the social and political aspects of “treatment” are more obvious-use of drugs for social control is explicit
Pathology of psychiatric conditions unknown

- Dopamine hypothesis of schizophrenia and monoamine hypothesis of depression derived from knowledge of drug action

- No conclusive independent evidence for them
The dopamine hypothesis of schizophrenia and psychosis
(Moncrieff, Harvard Review of Psychiatry, 2009)

- Atypical antipsychotics like clozapine have relatively low D$_2$ blocking activity

- Stimulant induced psychosis has not been pinned down to dopamine-other transmitters likely to be involved

- Total brain dopamine is normal (post mortem studies)

- Dopamine metabolites are normal

- Indirect measures of dopamine activity show differences in some studies, BUT have not controlled for other factors associated with dopamine activity such as movement, stress, attention, arousal and sometimes previous drug treatment.
Monoamine hypothesis of depression

• Antidepressant efficacy cited as main supporting evidence (Skildkraut 1965; Mahli et al, 2005)

• No consistent independent evidence of an abnormality of serotonin or noradrenalin in depression
Are neuroleptics superior to other sorts of sedatives?

- **Barbiturates**: 2 early studies showed chlorpromazine superior
- **Opium**: 1 study. Opium equal to chlorpromazine for acute psychosis
- **Benzodiazepines**: 6 trials: 3 trials AP=BZD; 2 trials BZD>AP; 1 trial CPZ>BZD=HAL
- **Lithium**: equal in moderately active cases, inferior in overactive cases (Braden et al, 1980).
Antidepressants are not very different from placebo

• Kirsch et al, 2002 meta-analysis: difference 1.7 points on HRSD

• Other recent meta-analyses similarly small differences (e.g. NICE, 2004).

• Differences easily accounted for by psychoactive effects of antidepressants

• Many other possible biases: publication bias, selective reporting, unblinding
Drugs that “improve” depression in clinical trials

- Buspirone
- Amphetamine
- Ritalin
- Alprazolam
- Diazepam
- Thioridazine (Melleril)
- Reserpine
- Other antipsychotics
- Dihydrocodeine
- Hypericum (St Johns wort)
Specificity of lithium for acute treatment

- Antipsychotics superior to lithium for very overactive patients with mania or psychosis, otherwise no difference (Prien 1972; Braden, 1982)

- Diagnosis does not effect treatment response (Braden et al, 1982; Johnstone et al, 1988)

- Clonazepam superior to lithium in small trial (Chouinard, 1988)
Lithium as prophylactic

• Placebo controlled trials confounded by discontinuation design

• Not clearly differentiated from other sedative drugs (antipsychotics and anticonvulsants)
Animal models of depression

- E.g. Forced Swim Test (FST), Chronic Stress Test
- Many “false positives” with non antidepressants e.g. stimulants, opiates, antipsychotics, atropine etc
- “false negatives”, especially SSRIs in the FST
Animal models of psychosis

- E.g. Conditioned Avoidance Response and reduction of stimulant induced stereotypies

- CAR response also obtained with benzos, histamine and toxins

- Stimulant induced stereotypy is a test for DA antagonism- clozapine and some other atypicals do not suppress it to same extent as older drugs.